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PARTICIPACION DEL NUCLEO SEPTAL LATERAL EN LAS ACCIONES DE LOS TRATAMIENTOS ANTIDEPRESIVOS

T E S I S

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p r e s e n t a:

M. en Psicobiol. Miguel Molina Hernández

Director de la Tesis: Dr. Carlos M. Contreras

Jurado: Dr. León Cintra McGlone
Dr. Carlos M. Contreras
Dr. Miguel Cervantes Alfaro
Dra. Dolores Rodríguez Ortiz
Dra. Matilde Valencia Flores
Dr. Roberto Prado Alcalá
Dr. Miguel Luján Estrada

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DEDICATORIA:

A mis padres: *Don Miguel Molina Luque y Doña Alicia Hernandez de Molina.*

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RESUMEN

Los trastornos de la afectividad son algunos de los síndromes psiquiátricos más frecuentes, ya que más de 150 millones de personas padecen depresión.

La depresión es un trastorno del estado afectivo caracterizado por un abatimiento motor y emocional. Se puede clasificar en dos tipos: la exógena y la endógena. El hecho de que los deprimidos se caracterizan por su incapacidad de experimentar placer, aunado a la existencia de porciones del sistema límbico llamadas de recompensa o de placer y puestas en evidencia por los fenómenos de autoestimulación, sugiere que estas estructuras están implicadas en la patofisiología de la depresión y en las acciones de los TAD.

Con base en lo anterior, se han planteado las siguientes hipótesis: A) el núcleo septal lateral es uno de los sitios de acción de los tratamientos antidepresivos; y B) la lesión neonatal del septum de la rata, constituye un modelo para producir un cuadro similar a la depresión endógena humana. El objetivo general de esta serie de experimentos es estudiar la participación del septum lateral en las acciones de los antidepresivos y su relación con otras estructuras del sistema límbico.

La administración de desmetilimipramina, de clorimipramina, del electrochoque y la privación de sueño incrementó la frecuencia de disparo de las neuronas del septum lateral pero sin tener acciones sinergistas. Y la lesión temprana del septum provocó mala ejecución de la prueba de nado en machos y hembras, pero las hembras resultaron menos afectadas y respondieron mejor a los tratamientos con antidepresivos, asimismo la lesión temprana del septum provocó que las neuronas inervadas por el rafe dorsalis conservaran sus propiedades farmacológicas después de la lesión.

Se concluye que el septum lateral de la rata es una estructura límbica que participa en las acciones de los TADs y que la lesión septal en etapas tempranas de la vida provoca cambios en su relación con otras estructuras límbicas y extralímbicas lo que implica alteraciones conductuales y farmacológicas en respuesta a la acción de los TAD, estos cambios se presentaron de manera dimórfica sexual.

Summary

Among other symptoms, in depression a blunted pleassure reactivity is commonly observed. Some authors suppose some relation with a failure in cerebral structures susceptible for experimental self-stimulation in lab animals. In such a case, same limbic structures might participate in the mechanism of action of the antidepressant treatments.

In present study four antidepressants drugs increased the firing rate in the lateral septal neurons of the rat however the acute combination of these treatments did not produce added effects. 24 hours of sleep deprivation blocked the actions of a single electroconvulsive shock. It is concluded that the firstly applied treatment modifies the receptors sensitivity from the very beginning, thus blocking the action of a second treatment.

In other experiments, several pharmacological maneuvers in very young rats produced later changes resembling human depression, and the possible changes induced by an early septal lesion in raphe-limbic neuronal activity are unknown. Rats were submitted to a wide lesion in lateral septal region at 8th day after birth and forced to swim at maturity. Male lesioned group showed the highest amount of immobility; whereas, female sham lesion group showed a greater response to treatments. We also evaluated the dorsal raphe-septal and -hippocampal single unit activity one year after the septal lesion. It is concluded that after early septal lesion, the hippocampal neurons appeared sensitive to desipramine administered by systemic route or locally by microiontophoresis and that the remaining septal neurons showed reversed patterns of response to desipramine administered by systemic or local route. In lesional groups, an increased amount of septal and hippocampal neurons showing an afterdischarge by dorsal raphe nucleus stimulation appeared which suggest a modified raphe-limbic innervation after early surgery. A gender-dependent sensitivity to early lateral septal nucleus lesions and to antidepressants are concluded.

Título

Participación del núcleo septal lateral en las acciones de los tratamientos antidepresivos.

Introducción

Los trastornos de la afectividad son algunos de los síndromes psiquiátricos más frecuentes, ya que su tasa de riesgo es del 14% en la población general. Sin embargo, sólo una minoría son tratados por psiquiátras o en instituciones psiquiátricas (242). La Organización Mundial de la Salud (OMS) reporta que más de 150 millones de personas padecen algún tipo de depresión (244) encontrándose mayor incidencia en mujeres de 20 - 25 años (243). Durante la adolescencia, pueden ocurrir pensamientos suicidas (245; 246), pero el suicidio es poco frecuente y predomina en el sexo masculino (247; 248). A cualquier edad, las mujeres son más susceptibles de cometer intentos de suicidio (249).

La conducta suicida está fuertemente relacionada con desórdenes psiquiátricos, tales como la depresión (250; 251; 252), lo que toma mayor relevancia en las personas de edad avanzada, ya que en esta población el riesgo de suicidio incrementa cuando se conjunta la depresión con la vejez (253). Por otra parte, del 12% de la población que recibe tratamientos antidepresivos (TAD) sólo algunos deprimidos llegan al suicidio (254).

La depresión es un trastorno del estado afectivo caracterizado por un abatimiento motor y emocional (255). Se puede clasificar en dos tipos: la exógena y la endógena. En la depresión exógena es posible demostrar relación entre el episodio depresivo y variaciones circunstanciales del entorno. Por el contrario, en la

depresión endógena o depresión mayor, los síntomas aparecen sin causa evidente y pueden recurrir. En ambos tipos de depresión se presenta ansiedad, sentimientos de frustración y de inferioridad, autodepreciación, enlentecimiento de las funciones psíquicas y psicomotoras, insomnio (7; 98), inseguridad, inestabilidad emocional y una intensa sensación de minusvalía, sin pérdida de la percepción de la realidad. Los deprimidos desean y buscan la muerte, y uno de los síntomas fundamentales es la anhedonia, la cuál se entiende como ausencia o pobreza de respuesta ante las contingencias medioambientales que regularmente producen una sensación de placer. Los deprimidos deben atenderse mediante TAD a base de fármacos y en algunos casos se emplea la terapia electroconvulsiva, sobre todo en aquellos con antecedentes de intento de suicidio.

El hecho de que los deprimidos se caracterizan por su incapacidad de experimentar placer (41; 92; 132), aunado a la existencia de porciones del sistema límbico llamadas de recompensa o de placer y puestas en evidencia por los fenómenos de autoestimulación (68; 140), sugiere que estas estructuras están implicadas en la patofisiología de la depresión y en las acciones de los TAD (34).

A pesar de numerosos trabajos efectuados en seres humanos y en animales experimentales, falta información concluyente en varios aspectos de la depresión, tales como: 1) la larga latencia existente entre la aplicación del TAD y el efecto terapéutico, además de que un 20% de los deprimidos son refractarios a los TAD

(75; 164); y 2) la alta incidencia de depresión que ocurre en las mujeres (217), pero tienen mejor respuesta a los TAD y menor tasa de suicidio (3).

Con respecto al primer punto, la depresión se asocia con alteraciones cerebrales de los sistemas de neurotransmisión (193), de tal manera que los TAD deben crear un balance nuevo de neurotransmisores, de receptores (13) y de segundos mensajeros (215). El que los TAD promuevan procesos plásticos (33; 76; 130) y regenerativos (129) explicaría la larga latencia para encontrar su efecto terapéutico.

Con respecto al segundo punto, varios aspectos de la fisiología y la conducta son sexo-dependientes (5), ya que el cerebro de las hembras presenta plasticidad diferente a los machos (17; 45; 46; 47; 86; 99; 106; 144; 179; 200; 209; 218). Las hormonas gonadales tienen receptores en varias estructuras límbicas (2; 18; 28; 90; 102; 107; 148; 152), participan en los estados depresivos (149) y en las acciones de los TAD (16; 162; 169). Se ha sugerido que las hormonas gonadales tienen acción antidepresiva (15) y ansiolítica (19), ya que la castración en ratas produce estados semejantes a la depresión (15; 16) y en modelos de depresión la función sexual está disminuida (131). Además, los TAD participan en la regulación hormonal (67; 103; 114; 118; 161; 176; 183).

Sin embargo, y a pesar de que la depresión es conocida desde hace siglos, aún se desconocen cuales son los sustratos anatomofucionales involucrados en este padecimiento. Una de las

hipótesis antiguas encaminadas a explicar las causas de la depresión fué propuesta por Schildkraut (1965), quien sugirió que la depresión es el resultado de un decremento en las aminas biógenas. La idea partió de la observación de que la administración de algunos antidepresivos resulta en un incremento de la disponibilidad de noradrenalina (NA) y serotonina (5HT) en el espacio sináptico.

Diversas estructuras límbicas han sido incluidas en la fisiopatología de la depresión. El sistema límbico es considerado como parte fundamental en la integración de mecanismos cerebrales relacionados con la conducta emocional. En la depresión existe una incapacidad o disminución en la capacidad para experimentar placer, por lo que se ha postulado que en la depresión puede haber una disfunción de las estructuras cerebrales responsables de la integración de la conducta emocional denominada placer, y por consiguiente, cabe la posibilidad de que los fármacos antidepresivos ejerzan su efecto modificando las características funcionales de estructuras límbicas. En especial, de aquellas relacionadas con el fenómeno de autoestimulación intracraneal.
Tal es el caso del septum (11), del hipocampo, del hipotálamo, de la amígdala y del área entorrinal, entre otras estructuras límbicas; así como sus conexiones con el locus coeruleus y los núcleos del rafe.

Anatomía

Núcleo Dorsal del Rafe

Se han localizado 8 núcleos del rafe, sus eferencias serotonérgicas inervan varias estructuras límbicas. Solo el rafe dorsal (NRD) y el medial (128) inervan al septum y al hipocampo por el haz medial mesencefálico (8; 9). El NRD se encuentra en la zona media y paramedia del pedúnculo cerebral y participa en la depresión (51; 52; 53); su estimulación eléctrica excita en el septum lateral (37; 38) e inhibe en la corteza cerebral (30; 36; 40; 178), en el cuerpo geniculado lateral (89), en el hipocampo (6; 20; 21; 170; 171; 172), en el locus coeruleus (26) y en el NRD (1; 146). Los TAD incrementan las acciones del NRD en corteza motora y en el septum lateral (36; 40).

Los núcleos del rafe tienen un pequeño número de somas celulares serotonérgicos pero poseen una amplia inervación del Sistema Nervioso (109). Actúan como puente conector entre diversos tipos de sensibilidad y varias estructuras del sistema límbico; asimismo se ha observado que la 5-HT que producen tiene efectos de neuromodulador (256) y de factor trófico (73). Los núcleos del rafe participan en la conducta alimenticia, la regulación de la temperatura, en el sueño, en los estados afectivos (257), en la conducta sexual, en la ansiedad y en los estados alucinatorios (257). Los núcleos del rafe se relacionan por medio de una rica inervación serotonérgica con diversas estructuras del sistema límbico, entre ellas el hipocampo y el septum (9). Empero, solo el rafe medialis y el dorsalis (128) se relacionan con el complejo

septal y el hipocampo tanto en sus conexiones aferentes como eferentes a través del tracto del cerebro anterior (8).

Las neuronas del NRD se pueden clasificar en tres tipos: fusiformes, multipolares y ovoideas. Las células fusiformes son las más frecuentes (48). Las neuronas del NRD presentan un patrón lento y regular de actividad espontánea, su frecuencia de disparo es de 1-2 Hz (77; 184; 230) y al igual que las neuronas del rafe medialis (231), poseen un sistema que acumula GABA, carente de conexiones monosinápticas, las que se consideran como conexiones intrínsecas (232). Las conexiones del NRD se clasifican en tractos ubicados ya sea por adentro o por fuera del haz medial del cerebro anterior (Cuadro 1).

Cuadro 1.- Tractos eferentes del NRD (*).

Tracto	Estructura inervada
Cerebro anterior	septum hipocampo
Cortical	corteza ganglios basales amígdala rafe medialis hipocampo n. caudado putamen corteza temporal corteza parietal
Medial	n. interpeduncular cuerpos mamilares
Arcuato	sustancia nigra hipotálamo
periventricular	tálamo hipotálamo

(*) según: (8); (9); (112); (141).

A nivel electrofisiológico, el NRD controla la presencia de un tipo de ritmo theta hipocámpico (150) y su estimulación produce modificación de los niveles de 5-HT en varias regiones del cerebro (175; 233) además de modificar la frecuencia de disparo en diferentes estructuras cerebrales (Cuadro 2). Algunas de sus terminaciones son dopaminérgicas (139; 207) e inervan al neoestriado (234), a la corteza prefrontal (224), al hipocampo (154), al tallo cerebral (173) y al septum (195).

Cuadro 2.-Acción electrofisiológica de la estimulación del NRD en la frecuencia de disparo de diferentes estructuras cerebrales.

Efecto	Estructura	Bibliografía
Inhibición (30)	corteza cerebral	(36; 40; 178)
	geniculado lateral	(89)
	hipocampo	(6; 20; 21;170; 171; 173; 228; 229)
	locus coeruleus	(26)
	NRD colaterales, receptor 5HT-1A	(1; 146; 177)
Aumento	septum lateral	(37; 38)

Septum

El septum es un componente del sistema límbico y participa en procesos motivacionales, asociativos, emocionales, reproductivos (96; 220), mnésicos (136), de aprendizaje y en los mecanismos cerebrales de la conducta hedónica (56). Además de ser un sitio de paso de las principales fibras que provienen del hipocampo y la amigdala y que van hacia el hipotálamo y tallo cerebral (197),

entre otras.

En los mamíferos (sin incluir primates), el área septal se encuentra situada por debajo de la porción anterior del cuerpo calloso y está rodeada por delante por el rudimento hipocámpico anterior y por detrás por la comisura del hipocampo.

El septum se puede dividir en cuatro regiones: la posterior, la ventral, la medial y la lateral (197). El septum lateral (NSL) constituye la porción dorsolateral del septum y se divide en tres subnúcleos: el dorsal, el intermedio y el ventral. Y recibe aferencias de varios núcleos cerebrales (104; 105; 189; 197) como son el locus coeruleus (57; 189), el NRD (9; 57; 195), el septum medial (4; 94), el núcleo intersticial de la stria terminal (57); el hipotálamo (12; 79) y el hipocampo (78), entre otras.

La región septal lateral, cuya cabeza empieza por debajo de la rodilla del cuerpo calloso se extiende hacia atrás a todo lo largo del área septal. La región septal medial, está unida con el área paraolfatoria y es extensión del tubérculo olfatorio. Hacia la región caudal, esta región se vuelve cada vez más pequeña y se une a la región septal lateral. Algunos autores, consideran como componentes de la región septal ventral al núcleo cama de la estría terminal, al núcleo accumbens septi y al núcleo de la banda diagonal de Broca (197). El septum, recibe aferencias de varios núcleos cerebrales (104; 105; 158; 159; 189; 197), como son la amígdala, el tálamo, el mesencéfalo y otras (Cuadro 3).

Cuadro 3.- Principales aferencias del septum lateral.

Estructura aferente	neurotransmisor	
locus coeruleus	noradrenalina (57; 189)	
núcleos dorsal y medial del rafe	serotonina (9; 57)	
septum medial	acetilcolina (4; 94)	
núcleo intersticial de la stria terminal	dopamina	(57)
Grupo A10		(208)
hipotálamo	encefalinas vasopresina somatostatina	(12) (241) (79)
hipocampo	aspartato glutamato	(78)
¿?	sustancia P	(235)

Asimismo el septum envía fibras hacia la habénula lateral y medial; en el tálamo inerva a los núcleos intralaminares, y al anteroventral y en la amígdala al núcleo basolateral. Asimismo a las cortezas del cíngulo, la orbitofrontal y la cerebral, al núcleo accumbens, al tubérculo olfatorio, a la taenia tecta, al hipotálamo, a la estria terminalis (189; 190; 197), a los núcleos del rafe (87), y al hipocampo (119; 120; 121; 235), entre otras.

El hallazgo de que el septum lateral es una de las estructuras en las cuáles los antidepresivos causan aumento del disparo celular (32; 34; 39) ha motivado para que nuestro grupo de investigación realice una serie de experimentos encaminados a investigar el papel que el septum lateral tiene en las acciones de los antidepresivos.

El NSL envía fibras colinérgicas (190) y GABAérgicas (78) al septum medial. Un 15% de neuronas del septum medial y un 17% de la banda diagonal de Brocca (49) envían fibras (94; 151) colinérgicas (11; 91; 174; 223) y GABAérgicas (54; 55; 70; 143) al hipocampo.

El hipocampo recibe información de varias estructuras cerebrales incluyendo el septum y envía eferencias monosinápticas excitatorias (60; 180; 194), mediadas por glutamato (58; 80) y aspartato (110) hacia el NSL, estas eferencias son ramas de la vía colateral de Schaeffer (198), se localizan de forma topográfica en el NSL y establecen sinapsis asimétricas en las espinas de las neuronas septales (4). En el NSL, la estimulación del hipocampo dorsal genera activación seguida de inhibición. La inhibición es producida por GABA (194), y es posible que se deba a la acción de colaterales que existen en las neuronas somatoespinosas del NSL (4; 153), esto sugiere la presencia de un sistema de retroalimentación en el NSL. Así, se establece un circuito cerebral *Hipocampo - Septum lateral - Septum medial - Hipocampo* (4; 101; 105; 124; 126; 196). Por otro lado, las eferencias colinérgicas del septum medial, en su paso hacia el hipocampo, envían fibras a las neuronas septales laterales que las inervaron (4) y actúan en receptores muscarínicos tipo 1 (74). En consecuencia, la regulación del disparo de las células somatoespinosas del NSL sería doble, por sus axones recurrentes y por las aferencias colinérgicas del septum medial (Figura 1).

Los núcleos septales y en especial el NSL funcionan como integradores-moduladores entre los núcleos septales y otras

estructuras cerebrales y afectan principalmente las funciones congnitivas procesadas por el hipocampo mediante la adición de un factor emocional a este tipo de funciones. Otra función importante de los núcleos septales es ejercer un papel crítico en el inicio, mantenimiento y expresión de la actividad eléctrica cortical (59). Esta actividad conocida como ritmo theta se modifica cuando existen desórdenes emocionales y afectivos.

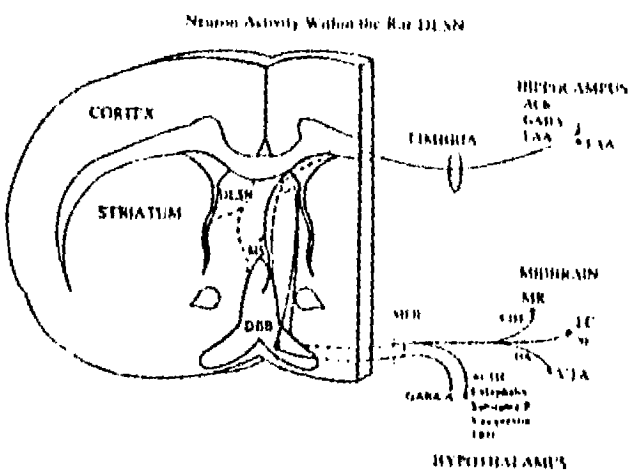

Figura 1.- Esquema de algunas de las conexiones del septum con otras estructuras del sistema nervioso central. Abreviaturas: DBB= banda diagonal de broca; MS= septum medial; DLSN= núcleo septal lateral; MFB = fascículo medio del tallo encefálico; MR = rafe medial; LC = locus coeruleus; VTA= área tegmental media: tomado de Gallagher et al., 1995 (59).

Modelo Electrofisiológico

Una forma de evaluar las acciones de los TAD en el sistema nervioso central es el análisis de sus acciones en la función sináptica. En este sentido, el exámen de la tasa de disparo neuronal, en las condiciones experimentales apropiadas, es un indicador de la función sináptica. De esta manera, nuestro grupo de investigación ha realizado una serie de experimentos encaminados a determinar los efectos de diferentes tratamientos antidepresivos eficaces en el ser humano, mediante el uso de la técnica de registro unitario extracelular en el área septal y algunas otras estructuras límbicas de la rata. Blier et al. (22; 23; 24) propusieron un modelo electrofisiológico para estudiar las acciones de los TAD en la vía serotonérgica y determinar la sensibilidad del autoreceptor. Así como la responsividad de las neuronas postsinápticas a la estimulación del NRD y su respuesta a la aplicación local de serotonina (5-HT).

En este paradigma se coloca un electrodo de estimulación en una región cerebral de la rata (región presináptica) y un electrodo de registro en otra región relacionada con la anterior (región postsináptica). De tal manera que en animales sometidos a la acción de TAD, ya sea de forma aguda o crónica, se obtienen registros bioeléctricos de la actividad de la neurona postsináptica, luego se estimula la región presináptica y se analiza su efecto, con esto se evalúa la relación entre las vías. Finalmente, se aplican antidepresivos *in situ* en la neurona en estudio y se determinan sus efectos en la tasa de disparo neuronal (Figura 2).

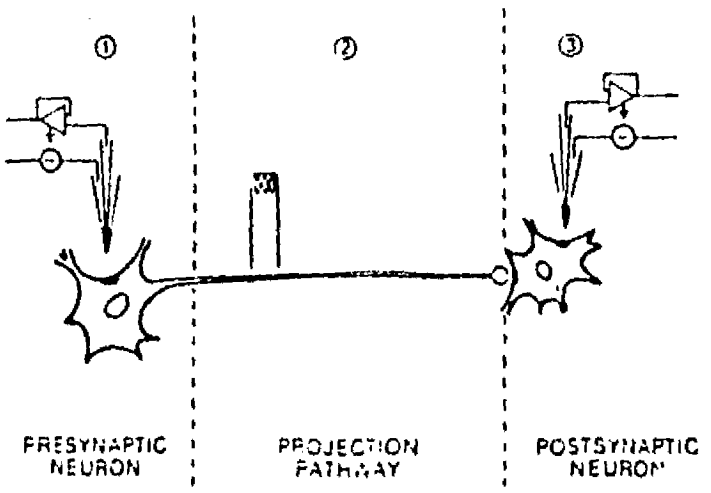

Figura 2.- Modelo de Blier: El paradigma propuesto es el estudio de la acción de los antidepresivos y la neurotransmisión serotonérgica. 1) Se estudia la actividad de la neurona presináptica y la sensibilidad de los autoreceptores somatodendríticos a la 5-HT; 2) efecto de la activación eléctrica de la vía ascendente serotonérgica en la neurona postsináptica y responsividad del autoreceptor terminal a 5-HT; 3) responsividad de la neurona postsináptica a la aplicación microiontoforética de 5-HT: tomado de Blier, et al., 1988 (23).

Registro Unitario Extracelular y la Tasa de Disparo Neuronal.

Se ha demostrado que es posible que los núcleos septales laterodorsal y lateral intermedio de la rata participen en las acciones de las terapias antidepresivas y en la fisiopatología de la depresión, ya que diversos antidepresivos, entre ellos, la CMI, administrados en forma aguda, incrementan la frecuencia de disparo de células septales (32, 76), fenómeno descrito también en el hipocampo (76). Asimismo, la administración crónica de fármacos antidepresivos (CMI, trazodona, isocarboxazida) y de tratamientos no farmacológicos, tales como el electrochoque y la privación del sueño, causan aumento de la frecuencia de disparo de las células del septum lateral, y alcanzan sus mayores efectos después de 16

días de tratamiento (34; 39). Asimismo, se ha demostrado que los antidepresivos tricíclicos incrementan el disparo en neuronas del septum lateral relacionadas con el hipocampo (113).

Contreras et al. (36; 40) demostraron que el tratamiento con CMI afecta la influencia de la vía serotonérgica del NRD hacia diferentes componentes del sistema nervioso central. Por ejemplo en la corteza motora de la rata, el antidepresivo provoca aumento de las respuestas inhibitorias de la vía rafe dorsalis - corteza motora (36; 40), de esto resulta incremento de la inhibición de la frecuencia de disparo de las neuronas corticales; en cambio, la estimulación del NRD aumenta la frecuencia de disparo de las neuronas septales laterales, efecto que es potenciado al aplicar CMI (36; 40).

En síntesis, el septum lateral es un componente del sistema límbico que participa en los fenómenos de autestimulación. Además, los antidepresivos incrementan la frecuencia de disparo de las células del septum lateral relacionadas con el hipocampo y aumentan los efectos que la estimulación del NRD tiene en estas células. Asimismo los antidepresivos provocan cambios en la neurotransmisión, en especial en la vía serotonérgica. Además, los pacientes deprimidos son incapaces de experimentar placer (41; 92; 132). Y por otro lado, la lesión del septum produce una variedad de alteraciones conductuales, tales como: hiper-reactividad a la estimulación sensorial, aumento de la evitación hacia choques eléctricos, hipoactividad locomotora y reducción del peso corporal (236; 237; 238; 239), estos síntomas varían en permanencia y

severidad, dependiendo de si el daño fué bilateral o unilateral, del espacio temporal de las lesiones, de la edad del sujeto, de su experiencia previa, de la localización y extensión de la lesión, entre otras (69; 236; 238; 240), además la lesión de otras estructuras cerebrales produce depresión (85). De tal manera que resulta válido sugerir la participación del septum lateral en la patofisiología de la depresión y en las acciones de los antidepresivos.

Con base en lo anterior, se han planteado las siguientes hipótesis de trabajo: A) el NSL es uno de los sitios de acción de los TAD; y B) la lesión neonatal del septum de la rata, constituye un modelo para producir un cuadro similar a la depresión endógena humana. El objetivo general de esta serie de experimentos es estudiar la participación del septum lateral en las acciones de los antidepresivos y su relación con otras estructuras del sistema límbico.

Progress in
Neuro-Psychopharmacology & Biological Psychiatry

Editor
Paul J. Bedard

Laboratory of Neuro-Psychopharmacology
Laval University Medical School
Québec
Canada G1K 7P4
Tel. +1 418 656 3508
Fax. +1 418 656 7818
email: PNPPBP@PHC.ULAVAL.CA

March 29, 1995

Dr. Carlos M. Contreras
P.O. Box 320
Xalapa 9100
Veracruz
MEXICO

our ref.: 940854

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The combination of several antidepressants is not synergistic on the firing of lateral septal neurons in the rat

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THE COMBINATION OF SEVERAL ANTIDEPRESSANTS IS NOT SYNERGISTIC ON THE FIRING OF LATERAL SEPTAL NEURONS IN THE RAT.

CARLOS M. CONTRERAS, DOLORES BELTRAN, MARGARITA SAAVEDRA and MIGUEL MOLINA-HERNANDEZ

Laboratorio de Neurofarmacología.
Instituto de Neuroetología, Universidad Veracruzana.
Departamento de Fisiología,
Instituto de Investigaciones Biomédicas,
Universidad Nacional Autónoma de México.
México.

(Final form, may 1995)

Abstract

Contreras Carlos M., Dolores Beltrán, Margarita Saavedra and Miguel Molina-Hernández. The Combination of Several Antidepressants is not Synergistic on the Firing of Lateral Septal Neurons in the Rat. Prog. Neuro-Psychopharmacol & Biol Psychiat. 1995: 19

1. Three kinds of antidepressants (clomipramine, sleep deprivation, and electroconvulsive shock) increase the firing rate in the lateral septal neurons of the rat.
2. The acute combination of these treatments, however, did not produce added effects on firing rate of lateral septal neurons in the rat.
3. 24 hours of sleep deprivation blocked the actions of a single electroconvulsive shock.
4. It is concluded that the firstly applied treatment modifies the receptors sensitivity from the very beginning, thus blocking the action of a second treatment.

Key words:antidepressants, clomipramine, electroconvulsive shock, lateral septal nucleus, sleep deprivation.

Abbreviations: clomipramine (CMI), electroconvulsive shock (ECS), lateral septal nucleus (LSN), sleep deprivation (SD).

Introduction

From non-drug antidepressant treatments, sleep deprivation (SD) is used efficaciously in some depressed patients (Vogel et al.

1980), and electroconvulsive shock (ECS) is considered the most effective alternative for depression not responding to drug treatment (Fawcett and Scheftner, 1986); herein, clomipramine (CMI) is a tricyclic still used as an antidepressant in some countries, and currently in the treatment of phobic and obsessional states (Healy, 1991).

Anhedonia is one the main ailments in depression, and the lateral septal nuclei (LSN) are limbic structures considered among the reward systems in the brain (Olds and Milner, 1954); this suggests some relation between reward systems in the brain, intracranial self-stimulation, antidepressants and depression. Incidentally, the long-term treatment with CMI increases the firing rate in neurons from LSN of the rat (Contreras et al. 1990), whereas the intracranial septal self-stimulation rate increases after long-term treatment with tricyclics (Fibiger and Phillips, 1981). The acute injection of CMI, one ECS or 24 hours of SD increase the firing rate in LSN with different potency (Contreras et al. 1989); however, it is unknown whether these treatments are synergistic. A first step in answering the question was undertaken by studying the interaction of acutely applied SD, CMI, and ECS in affecting the LSN firing rate.

Material and Methods

Animals

Male adult (250-300 g) Wistar rats locally bred, maintained in housing facilities with an artificial light/darkness cycle of 12:12 hrs, and water and food *ad lib* were included in the study.

Treatments

Ten different groups received different schedules of treatments, except the first, free of any treatment (control). A second group received a single ECS, a third a single injection of CMI, and a fourth was sleep deprived during 24 hours. Other groups received

two treatments in alternated sequences. Two groups were sleep deprived during 24 hours and then received a single ECS (fifth group), or a single CMI injection (sixth group). Two other groups firstly received CMI; one was immediately submitted to SD (seventh group), and the other received a single ECS one hour after CMI injection (eighth group). Finally, two more groups received a single ECS as the first treatment, then were injected with CMI (ninth group), or were sleep deprived for the next 24 hours (tenth group).

The second, fifth, eighth, ninth and tenth groups received an ECS (1.0 msec, 100 Hz, 50 μA) applied through displaceable metallic pins inserted in the auditory meatuses. The duration of the ECS was determined by hyperextension of the forepaws which signaled the beginning of a tonic-clonic seizure (roughly 20 sec duration). The reappearance of righting reflexes indicated the CMI injection, or beginning of SD, or surgery.

Rats from fourth, fifth, sixth, seventh and tenth groups were placed during 24 hours (8:00 AM), one at a time, in a plexiglass box (45 cm X 24 cm X 20 cm) with a tensed wire 2 cm above water level (6 cm). No time for natural sleep was allowed, since surgery or another treatment began just after 24 hours of SD.

In the third, sixth, seventh, eight and ninth groups, CMI (1.25 mg/kg i.p.) was injected one hour before surgery, ECS or SD.

Procedure

Urethane was used as anaesthetic (1.2 g/kg, i.p. as initial doses, and one fifth every 2 h), and lidocaine (2 %) was infiltrated into surgical wounds. Single unit extracellular recordings began 2-3 hours after the first injection of urethane. An electrolytically sharpened stainless steel microwire (4 μm, 1 MΩ resistance) was stereotaxically positioned in LSN (0.3 mm AP, 0.5 mm L, and 3.0-5.0 mm from the cortical surface). The electrode was connected to a Grass P-15 preamplifier (bandwidth filters: 3 Khz,

300 Hz; gain X 1000) which feed the output signal to an oscilloscope, an speaker, and a personal computer. The neuronal activity was analyzed using interval histograms and statistical mean of firing.

Data Analysis

At the end of recordings DC current (0.1 mAmp) marked the first and last recorded points, then the animals were sacrificed by a lethal dose of pentobarbital, and their brains intracardially perfused with Kornosky solution for later verification of the recorded places by freezing sections. Data were commonly obtained from no less than three cells per animal; in consequence, the path followed by the electrode was reconstructed from histological data and stereotaxic readings. Statistics used the ANOVA test and only included those recordings identified as taken in LSN. *Post hoc* analysis used the Dunnet test.

Results

A total amount of 485 recordings were identified as taken from LSN. All treatments produced a significantly increased firing rate ($F_{9,425} = 5.186$, $p < 0.01$), similar to the change in firing rate produced by a single injection of CMI or 24 hours of SD, but significantly lower ($p < 0.05$) than one ECS (Table 1).

In regard to the combinations, neither SD nor ECS applied after CMI produced any additional change in the LSN neuronal firing rate. Similarly, when SD was the first applied treatment, CMI failed to produce additional changes. In rats in which SD preceded an ECS, the remarkable increase in firing rate produced by the single isolated effect of one ECS disappeared.

Table 1.

Firing Rate in Dorsal Aspect of LSN after Treatments and Their Combinations.

	Firing rate (mean ± SEM)	N
Control	2.91 Hz ± 0.25	100
CMI	4.72 Hz ± 0.44*	78
CMI+ECS	5.35 Hz ± 0.73*	34
CMI+SD	5.35 Hz ± 0.73*	46
SD	4.67 Hz ± 0.59*	44
SD+CMI	4.53 Hz ± 0.56*	40
SD+ECS	4.23 Hz ± 0.66*	34
ECS	7.21 Hz ± 0.73*,+	32
ECS+SD	4.85 Hz ± 0.62*,++	44
ECS+CMI	6.81 Hz ± 1.50*	33

*: $p < 0.05$ against control, +: $p < 0.01$ between first treatments, ++: $p < 0.01$ against first treatment.

ECS proved to be the most potent treatment in producing an increased firing rate ($p < 0.001$), and the change in firing rate remained at similar values when CMI was the second treatment. Nonetheless, 24 hours of SD after one ECS blocked the effects of one ECS.

Discussion

The combination of treatments failed to produce added effects; moreover, conflicting actions appeared for the second treatment, suggesting that the firstly applied treatment had strongly affected receptors from the beginning. Indeed, the three treatments studied

produce acute relevant actions whose meaning from a clinical perspective is unknown. ECS causes a significantly increased noradrenergic plasmatic level some minutes after the first ECS and is not followed by any cumulative effect (Mann et al. 1990). In the case of sleep deprivation: a) a worsening of symptomatology follows each night of normal sleep (Holsboer-Trachsler and Ernst 1986); b) a single dose of another tricyclic, imipramine, reverses the sleep disturbances (Kupfer 1989); and c) the strong REM sleep reduction produced by CMI disappears as treatment progresses (Kupfer et al. 1989).

The remarkable increase in neuronal firing produced by ECS was reduced by combining the ECS with a 24-hour period of sleep deprivation, regardless of sequence. Sleep deprivation has been proposed as the main mechanism of action in antidepressant treatments (Vogel et al. 1990); in such a case, added effects of SD could be expected when combined with other treatments; however, in the present study no added effects appeared. Consistently, no substantial relationship between clinical response to CMI and the amount of REM sleep suppression had been observed (Riemann and Berger 1990); and trimipramine, in spite of being an effective antidepressant, does not suppress REM sleep (Wiegand et al. 1986). Lastly, sleep deprivation is a weaker treatment than CMI in producing an increased firing rate in LSN (Contreras et al. 1993). Taken together, these data suggest that sleep deprivation may be a common feature but not the main action of antidepressant treatments.

Conclusion

CMI, SD, and ECS increased the firing rate in LSN neurons, but the combination of treatments failed to produce added effects. A deleterious interaction of SD with ECS also emerges as a conclusion.

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Inquiries and reprint requests should be addressed to:

Dr. Carlos M. Contreras
POB 320 Xalapa 91000
Veracruz. México

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C.M. Contreras et al.
Running Title
Non-synergistic action of antidepressants

Progress in
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Editor
Paul J. Bedard

Laboratory of Neuro-Psychopharmacology
Laval University Medical School
Québec
Canada G1K 7P4
Tel. + 1 418 656 3508
Fax. + 1 418 656 7818
email: PNPPBP@PHC.ULAVAL.CA

Quebec, April 5, 1995

Dr. Carlos M. Contreras
POB 320
Xalapa 91 000
Veracruz
Mexico

our ref.: 940855

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An early lesion of the lateral septal nuclei produces changes in the forced swin test depending on gender

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AN EARLY LESION OF THE LATERAL SEPTAL NUCLEI PRODUCES CHANGES IN THE FORCED SWIM TEST DEPENDING ON GENDER.

CARLOS M. CONTRERAS, HORACIO LARA-MORALES, MIGUEL MOLINA-HERNANDEZ, MARGARITA SAAVEDRA, and GERARDO ARRELLIN-ROSAS

Laboratorio de Neurofarmacología. Departamento de Fisiología, Instituto de Investigaciones Biomédicas, UNAM.
Instituto de Neuroetología, Universidad Veracruzana,
México

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Abstract

Contreras Carlos M., Horacio Lara-Morales, Miguel Molina-Hernández, Margarita Saavedra and Gerardo Arrellín-Rosas. An Early Lesion of the Lateral Septal Nuclei Produces Changes in the Forced Swim Test Depending on Gender. Prog. Neuro-Psychopharmacol & Biol. Psychiat. 1995, 19

1. Several pharmacological maneuvers in very young rats produce later changes resembling human depression.
2. Rats were submitted to a wide lesion in lateral septal region at 8th day after birth and forced to swim at maturity.
3. Male lesioned group showed the highest amount of immobility; whereas, female sham lesion group showed a greater response to treatments.
4. A gender-dependent sensitivity to early lateral septal nucleus lesions and to antidepressants are concluded.

Key words: clomipramine, early lesions, electroconvulsive shock, forced swim test, lateral septal nuclei, plasticity.

Abbreviations: clomipramine (CMI), electroconvulsive shock (ECS), 6 hydroxy-dopamine (6-OHDA), lateral septal nuclei (LSN), N-methyl-D-aspartate (NMDA), rapid eye movements (REM).

Introduction

The injection of CMI or desipramine in very young rats produces a supposed early REM sleep suppression related to some behavioral abnormalities at maturity resembling the human endogenous depression (Hilakivi and Hilakivi, 1987; Neill et al., 1990; Vogel and Vogel, 1982; Vogel et al., 1988; 1990a; 1990b). Nonetheless, in

adult rats the continuous infusion of maprotiline or desipramine into the previously lesioned (6-OHDA) frontal cortex, induces regeneration of noradrenergic axon terminals (Nakamura, 1990) suggesting that the previous state of the receptors, including maturity, influences the actions of tricyclics.

In the adult rat several antidepressant treatments produce an increased neuronal firing rate in LSN (Contreras et al. 1990; 1991; 1993); however, it is unknown whether early lesions in these nuclei impinge on the later performance of a test used for assaying antidepressants (Porsolt et al., 1977). Therefore, very young rats were submitted to a wide lesion of the lateral septal nuclei and forced to swim at maturity.

Material and Methods

Experimental Procedure

In dissections carried out in matched pups (8th day after birth), the lateral septal area was located 0.5 mm from the midline, and 2.5 mm below the bregma suture. Under slight anaesthesia with ether and while kept on a cold surface, one hundred Wistar pups were submitted to surgery. In one half of the animals (lesioned groups), direct current (2.5 mAmps) was applied to each lateral septal nucleus through a stainless steel wire (100 μm diameter), epoxy-isolated throughout except for the distal ending (1 mm). Cyanoacrylate closed surgical wounds, and a small mark on the ear allowed further identification of groups. The other half of the pups was submitted to a similar procedure, except for direct current delivery (sham lesion groups). The pups conformed randomized litters until the 25th day after birth, when they were grouped by sex and surgical procedure and maintained in housing facilities with a light/darkness cycle of 12/12 hours, and water and food *ad lib*. The weight gain was assessed weekly. At three months of age, 60 animals of similar weight (about 300 gr each) were distributed to integrate two sham-lesion groups (15 male, 15

female) and two lesioned groups (15 male, 15 female).

Behavioral Study

In a first 15-min training-session excluded from analysis of data, the rats were forced to swim in a rectangular aquarium (24 X 50 X 30 cm) filled with water at 25 °C to a height of 18 cm from the bottom. In the following 5-min test sessions, immobility was assumed when the rats touched the bottom of the aquarium with two hindpaws or one hindpaw plus the tail. After swimming, the rats were placed in a dry chamber at 30 °C, and lastly returned to housing facilities. The number of periods, the total time, and the latency to the first period of immobility were evaluated by three observers unaware of the grouping and treatments. Only three coincident observations were taken into account for analysis of data. The number of feces was also counted.

A longitudinal design allowed comparison of data using the animals as their own control. For each rat, the first test was applied in absence of any treatment (CTRL), the second at finishing a CMI regimen (CMI-1: 2.5 mg/kg i.p., twice a day, during 28 days), and the third after a 28-day period of saline (SAL-1: 0.12 ml i.p. twice a day). The fourth test was applied upon finishing a second CMI regimen (CMI-2: 5 mg/kg, i.p., twice a day, during 28 days) and the fifth test after finishing another saline treatment (SAL-2: 0.12 ml i.p. twice a day). A 28-day period free of any treatment preceded the sixth and last swimming session which was applied after one ECS, once the rats had recovered their righting reflexes (roughly 10 min). A behavioral seizure (10-20 sec duration) was produced by rectangle pulses (50 mAmps AC, 100 Hz, 1 msec) applied through displaceable metallic pins inserted into the auditory meatuses.

Finally, the rats were sacrificed by a lethal dose of pentobarbital, and perfused with formalin (20%) by cardiac approach. Their brains were extracted and allowed to sink for freezing sections and Nissl technique.

Data Analysis

The Pearson matrix was applied and the analysis of data compared immobility and number of feces by surgery and gender using Student's *t* test, repeated measures ANOVA and Tukey test as *post hoc*. The results are expressed as the mean ± S.E.

Results

A significative correlation was found between the latency to the first period of immobility, the total time ($r = -0.835$; $p < 0.01$), and the number of periods of immobility longer than 1 sec ($r = -0.766$; $p < 0.01$). Therefore, from the swimming test only data from the number of immobilities are presented.

Table 1.

Number of Periods of Immobility Longer than One Sec in Male Groups.

	CTRL	*CMI-1*	*SAL-1*	*CMI-2*	*SAL-2*	*ECS*
SHAM♂	*16.4±1.5*	*14.0±1.1*	*14.3±1.0*	*15.9±1.3*	*11.3±1.0**	*11.3±1.3**
LES♂	*21.1±1.5***	*13.3±1.2**	*11.9±1.3**	*12.3±1.4**	*11.1±1.1**	*4.3±1.4*,***

* *p < 0.05, against control: CTRL*
** *p < 0.05, surgery*

The male lesioned group (Table 1) showed the highest amount of immobility ($p < 0.05$) before any treatment (CTRL) with respect to all other groups. All treatments significantly reduced immobility in both the sham-lesion group ($F_{5,85} = 2.40$, $p < 0.05$) and the lesioned male group ($F_{5,85} = 13.52$, $p < 0.001$), but in the sham-lesion group a significative ($p < 0.05$) decrease in immobility appeared only after discontinuation of the high regimen of CMI (SAL-2) and after one ECS.

Table 2.
Number of Periods of Immobility Longer than One Sec in Female Groups.

	CTRL	*CMI-1*	*SAL-1*	*CMI-2*	*SAL-2*	*ECS*
SHAM♀	*14.6±1.1*	*15.0±1.5*	*12.5±1.6*	*9.1±1.5**	*8.7±1.3**	*3.3±0.8**
LES♀	*17.9±1.5*	*10.4±1.1*,***	*12.8±1.3**	*9.9±1.9**	*8.6±1.6**	*3.4±1.0**

** p < 0.05, against control: CTRL*
*** p < 0.05, surgery*

The immobilities in the female sham-lesion group (Table 2) decreased after the high regimen of CMI, an effect endured for the next 28-days period of saline treatment (SAL-2), and became more pronounced ($p < 0.01$) after one ECS. The female lesioned group reduced immobilities ($p < 0.05$) after each treatment, including the low regimen of CMI.

A significative ($p < 0.05$) decrease of immobility appeared in the sham-lesion female group after the high regimen of CMI ($p < 0.05$) and one ECS ($p < 0.001$) as compared to the sham-lesion male group. Lesioned groups showed no significant differences related to gender once they had been submitted to treatments.

A weak but significant correlation between the number of immobilities and the number of feces appeared ($r= -0.586$, $p < 0.05$). In the control session, the male lesioned group showed a significative ($p < 0.05$) higher number of feces than the male sham-lesion group. Treatments produced changes in the number of feces in the male sham-lesion group ($F_{5,85}= 3.75$, $p < 0.03$), and in the female lesioned group ($F_{5, 85}= 2.52$, $p < 0.02$). In the male sham-lesion group the high regimen of CMI produced a significant ($p < 0.05$) increase in the number of feces; whereas, in the female lesioned group, both CMI treatments and ECS significantly decreased the number of feces (Table 3). No differences in the number of

feces were observed in the female lesioned group as compared to its sham-lesion counterpart.

Table 3.

Number of Feces During the Five Min in Which the Animals Were Forced to Swim.

	CTRL	*CMI-1*	*SAL-1*	*CMI-2*	*SAL-2*	*ECS*
SHAM♂	*3.2±0.4*	*4.4±0.4*	*4.7±0.4*	*6.1±0.8**	*5.4±0.7*	*4.1±0.7*
LES♂	*5.1±0.6*	*4.2±0.5*	*4.8±0.5*	*4.9±0.5*	*5.0±0.4*	*3.0±0.7*
SHAM♀	*5.4±0.5*	*5.5±0.6*	*5.0±0.5*	*3.7±0.8*	*5.1±0.6*	*3.9±0.7*
LES♀	*6.2±0.5*	*4.7±0.4**	*5.0±0.5*	*4.0±0.9**	*4.0±0.7**	*4.1±0.6**

* *p < 0.05 against control*

Histology

In both the sham and lesioned groups the cranial bone and the cortical surface above the place of penetration of the electrode appeared displaced towards the basis of the brain. Gross histology showed that the lesion involved the dorsal and intermediate portions of LSN, including the rostral portion of the triangular and medial septal nucleus. The hippocampus appeared reduced in size, giving an aspect of dilatation of the third and lateral ventricles. The neuronal size and gross structure in the remaining portion of the septal area appeared normal, with some degree of gliosis and neuronal devastation. These features appeared similar in male and female groups.

Discussion

Early Surgery

A wide early lesion in LSN related to a greater amount of immobilities at maturity. At one week of age, the hippocampal cells

possess a marginal hyperpolarizing response to serotonin without intrinsic inhibitory potentials (Segal, 1990) which emerges several weeks later (Michelson and Lothman, 1989). Nonetheless, since in hippocampal slices an increased activity of the nerve growth factor occurs as far as one year after medial septal lesion (Collins and Crutcher, 1989), the failures in swimming at maturity could be attributed to the lesion practiced on the 8th day after birth, in a system not yet mature, but during an evenly sustained effort of the brain to recover from lesion.

Swimming sessions began at three months of age and concluded some months later. However, the influence of age may be discarded as a relevant factor, since data were compared between animals matched as to age and gender. Moreover, the sham-lesion male group showed the least effect from last treatment (ECS) , but this group responded poorly to all treatments.

Gender Differences.

The animals were tested at the third month after birth, once sexual maturity had been achieved. In similarly aged but healthy rats, the administration of human antidepressants may increase courage, thus reducing the immobility in rats forced to swim (West, 1990); however, in early lesioned rats additional effects may be expected.

Some sexual dimorphism occurs in depression and in the response to antidepressants. Albeit women are the prime consumers of antidepressants (Weissman and Klerman 1977), a higher suicide rate among males than females occurs (Farmer 1992). Let us assume that some aspects of the sensitivity to antidepressants depend on the level of steroidal hormones: a) the ovariectomy followed by estrogen replacement brought about a small but significant increase of NMDA receptor mRNA levels in the cerebral cortex (Brann et al., 1993); b) the levels of this cerebral steroidal receptor increase in the presence of estradiol (Bettini et al., 1992); and c) long-term imipramine, citalopram and ECS produce long-lasting adaptive changes in the NMDA receptor (Paul et al., 1994). The NMDA receptor

represents, therefore, a common place of action for steroidal hormones and some antidepressants, which may explain the observation that CMI and ECS reduced immobility in sham-lesion females more efficaciously than in sham-lesion males. A decreased immobility with a low number of feces may be globally interpreted as reduced anxiety. Male lesioned groups, on the contrary showed, the highest immobility and the highest number of feces before treatments, suggesting an increased anxiety and a diminished effort to scape from the stressful situation represented by forced swimming, in a gender-dependent fashion.

Conclusion.

An early lateral septal lesion produces immobility in the forced swim test mainly in male rats, whereas female groups prove to be better responders to human antidepressant treatments. A gender-dependent sensitivity to early lesions and antidepressants is concluded.

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Inquires and reprint requests should be addressed to:

Dr. Carlos M. Contreras.
POB 320, Xalapa 91000, Veracruz,
México.

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Running Title
Early Lesion and Swimming Test

UNIVERSIDAD NACIONAL AUTÓNOMA DE MEXICO

INSTITUTO DE INVESTIGACIONES BIOMEDICAS
APARTADO POSTAL 70228
CIUDAD UNIVERSITARIA
04510 MEXICO D.F.

Dr. Swan Chawla
Associate Editor
PROG NEURO-PSYCHOPHARMACOL & BIOL PSYCHIAT
Department of Pharmacology Pavillon Vandry
Laval University Medical School
Québec, Canada GIK 7P4
FAX 95 1 (418) 656 7818

Dear Dr. Chawla: 28 april 1995

Enclosed are two copies of "Changes in raphe-hippocampal and -septal neurons after a neonatal septal lesion (PN8) in the rat" by Molina et al. The paper is submitted to be considered for publication as a "research report" in your journal. Neither the entire paper nor any part of its content has been accepted by another journal. The paper is not being submitted to any other journal.

We believe that the paper may be of particular interest to your readers because the study reports some electrophysiological studies in early lesioned septal rats. This study complements one which is going to be published in your Journal. In that study we demonstrated some behavioral alterations after early limbic lesions in rats. Present study reports that limbic neurons related with dorsal raphe nucleus preserved their pharmacological properties.

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Thank you for your attention to our paper.
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Changes in raphe-hippocampal and -septal neurons after a neonatal septal lesion (PN-8) in the rat.

Miguel Molina, Jose Luis Díaz, Margarita Saavedra,
Maribel Ortiz and Carlos M. Contreras

Laboratorio de Neurofarmacología. Departamento de Fisiología, Instituto de Investigaciones Biomédicas, UNAM.
Instituto de Neuroetología, Instituto de Investigaciones Psicológicas, Universidad Veracruzana.
México

(Final form,)

Abstract

Miguel Molina, Jose Luis Díaz, Margarita Saavedra, Maribel Ortiz and Carlos M. Contreras. Changes in raphe-hippocampal and -septal neurons after a neonatal septal lesion (PN-8) in the rat. Prog. Neuro-Psychopharmacol & Biol Psychiat. 1995:

1. The possible changes induced by an early septal lesion in raphe-limbic neuronal activity are unknown. Therefore, in Wistar female rats submitted to a wide lesion in lateral septal region at 8th day after birth, the dorsal raphe-septal and -hippocampal single unit activity was evaluated one year thereafter.

2. It is concluded that after early septal lesion, the hippocampal neurons appeared sensitive to desipramine administered by systemic route (2.14 mg/kg, i.p.; during 21 days) or locally by microiontophoresis (10-15 nAmps, 0.5 seg).

3. The remaining septal neurons showed reversed patterns of response to desipramine administered by systemic or local route.

4. In lesional groups, an increased amount of septal and hippocampal neurons showing an afterdischarge by dorsal raphe nucleus stimulation appeared which suggest a modified raphe-limbic innervation after early surgery.

Key words: desmetilimipramine, early septal lesion, lateral septal nuclei, limbic, hippocampus, dorsal raphe nucleus.

Abbreviations: Desipramine (DMI).

Introduction

In spite of the fact that women are the prime consumers of antidepressants (Weissman et al., 1977) and also that depression appears mainly in women (Hawton, 1982), the highest amount of

relative literature uses male groups as experimental animals. Hence, the inclusion of female groups in the studies dealing with antidepressants and depression must be taken into account.

The dorsal raphe nucleus-limbic neuronal system is involved in the antidepressant actions. Long-term tricyclic drugs administration produces in the rat an enhancement of the excitatory action of the dorsal raphe nucleus on lateral septal neurons (Contreras et al., 1993b) and on the inhibitory actions of the raphe-cortical (Contreras et al., 1993a), or the raphe-hippocampal neurons (Blier et al., 1988).

The neurons from lateral septal nuclei increases their firing rate after both systemic (Contreras et al., 1990) long-term or acute intraventricular clomipramine administration (Contreras et al., 1989); hence, lateral septal neurons seems to be involved in the actions of antidepressants. Herein, a neonatal septal lesion causes a gender-dependent increased immobility in rats forced to swim at maturity. This effect is reversed by antidepressants mainly in female groups which also are less affected by the early septal lesions than male groups (Contreras et al., 1995). However, it is unknown whether a neonatal septal lesion influences raphe-limbic connections at maturity; therefore, very young female rats suffered a wide lesion in lateral septal nucleus at 8th day after birth for evaluation of raphe-limbic electrophysiological activity one year after.

Material and Methods

Design

In female rats a lesion was practiced on lateral septal nucleus a few days after birth and tested at maturity, thus conforming three groups of rats. The control group did not receive any surgery nor treatment; sham lesion group received non-lesional surgery a few days after birth and DMI before electrophysiological testing, and lesion group which having being lesioned at birth later received a long-term treatment with DMI. At maturity, peristimulus histograms allowed the identification of raphe limbic connections by evaluating the kind of afterdischarge into three

categories: septal and hippocampal afterdischarging neurons, non-late responder neurons, and neurons inhibited after dorsal raphe nucleus stimulation. Finally, rats received DMI applied by microiontophoresis in septal or hippocampal neurons from rats sham-lesional or septal lesion rats, long-term treated with DMI, and control rats saline-treated but surgically intact.

Early Septal Lesion

The method has already been described (Contreras et al., 1995). A small current (D.C., 2.5 mA, 10 s) is applied to lateral septal nucleus through a stainless steel microwire (100 μM diameter) placed in the lateral septal nucleus of pups (8th day after birth) slightly anesthetized with ether and maintained in a cold surface. The skin is confronted and the incision closed with cyanoacrylate. The sham group receives identical procedure except for D.C. current.

Drug Treatments

One year after the early septal lesion, two groups composed by sham (n=7) and lesion female rats (lesion, n=7) received DMI (2.14 mg/kg, i.p.; during 21 days). Selection of dose based on the extrapolation of previous results with tricyclics (Contreras et al., 1989). Another surgically intact female group (control-saline, n=15) received an equivalent volume of saline (0.15 ml, i.p., during 21 days). In all groups, the last injection preceded the surgery and the electrophysiological recording for about two hours.

Adult Surgery

The rats were anaesthetized by receiving ethylcarbamide 1.2 g/kg (i.p.) as an initial dose and one fifth of this amount every hour throughout the recording. Special care was taken into account for injecting lidocaine (2%) in the pressure points of the stereotaxic instrument and in the surgical wounds.

Electrophysiological Recording

Borosilicate pipets (NaCl, 2M; Evans blue, 2.5%; DMI, 2 nM) yielded single unit extracellular recordings. A hydraulic micromanipulator allowed the stereotaxic placement of electrodes in the ventral portion of lateral septal nucleus (AP=9.0 mm, L= 0.1

mm, H= 3-5 mm beneath the cortical surface) or CA1-CA3 (AP= -2.8, L=1.9, H=2.5 - 4.0). The obtained signal feeded a DAGAN amplifier, an oscilloscope, an audio system and a PC equipped with programs for peristimulus histogram and time-frequency graphs, as well as statistical mean of firing rate (± error standard).

Electrical Stimulation

A bipolar stainless steel concentric electrode (tip: 50 μm, resistance: 100 KΩ, wide: 0.3mm) was directed to the dorsal raphe nucleus (AP= +1.2, L = 0, H= +3.2). Gelfoam rapidly controlled the bleeding of venous sinus, and the vigorous response of multiple unit activity in response to reverse-hair-insertion brushing confirmed the accuracy of electrode placement.

Data Collection

A five-min period of stabilization of recording followed any single neuron impaling. A PC program capted 1000 spikes as control recording and delivered frequency and interval histograms, as well as statistical mean of firing. Then, dorsal raphe nucleus was stimulated (squared pulses: 0.1 mAmp, 0.3 Hz, 0.5 ms width) and another 1000 spikes accumulated. Peristimulus histograms (bin time 0.3 ms) classified the responses to the dorsal raphe nucleus stimulation.

Lastly, frequency-time graphs of neuronal firing (1 min, control) evaluated the actions of DMI (4 min) locally applied by microiontophoresis (10-15 nAmps, 0.5 seg) on the identified raphe-septal or -hippocampal neuron.

Histological Control

At the end of recordings the last recorded and the stimulated points were marked through current applied by the recording (D.C., 1000 nA, 30 s) and the stimulating (D.C., 10 mAmp, 60 s) electrodes. The rats were intracardially perfused with formalin (10%) and their brains freezed and cut (80 μm). Since for each animal more than five neuronal recordings were obtained, the path followed by the electrode was reconstructed by the marks left and the stereotaxic coordinates using Nissl staining technique.

Results

Histological Control

In all animals included in analysis of data, the stimulating electrode was located in the protuberancial area just bellow the periacueductal gray substance, precisely in the dorsal raphe nucleus. In the septal remanent, the recording electrode was located in the most basal portion of these nucleus, above the anterior commissure and in the inner portion of an expanded lateral ventricle. The hippocampal recording electrode was located in CA1-CA3.

In the lesion animals, the size of the septal area appeared reduced, giving an aspect of dilatation of the third and lateral ventricles. The hippocampus appeared reduced in its upper-lower axis, giving together with the atrophic zone in lateral septal nucleus the aspect of hypertrophy to lateral ventricles. The cellular framework appeared preserved in both limbic structures.

Recording

We recorded a total amount of 93 neurons from lateral septal nucleus, and 128 from hippocampus; non significant differences in the amplitude of recorded neurons between the different experimental groups appeared. The amplitude of recordings of lateral septal nucleus in control-saline (283.6±36.9), the sham (281.4±31.5) and the lesion (293.8±71.0) groups differ non significantly. Similarly, the amplitude of recordings from hippocampal neurons oscillated in a non significant manner in the control-saline (296.1±32.5), sham (385.3 ±53.0) and lesion (417.8±174.2) groups.

Dorsal raphe nucleus Stimulation

The dorsal raphe nucleus stimulation produced an initial paucisynaptic response in the lateral septal nucleus (latency 8.5 ± 0.4 ms, duration 9.7 ± 0.65 ms) and in the hippocampus (latency 10.2 ± 1.91 ms, duration 12.9 ± 1.5 ms), which preceded an afterdischarge in 20.4% from the total amount of neurons recorded in lateral septal nucleus, and 16.1% from hippocampus. In most of recordings from lateral septal nucleus (69.9%) or hippocampus (47.7%) only the initial response appeared (non-late responder

neurons). Lastly, in the fewest recordings an inhibition period appeared in a reduced amount, restraining the statistical analysis (lateral septal nucleus: 9.7%; hippocampus: 6.2%) and excluding this later group from analysis of data.

The percentages of afterdischarging and non-late responder neurons distributed differently depending on the group of treatment and surgery. The amount of septal afterdischarging neurons in the lesion proved to be threefold, as compared with control-saline or sham groups. A similar proportion appeared in hippocampus (Table 1).

Table 1.
PERCENTAGE OF RESPONSES TO DRN STIMULATION (%, n).

		Afterdischarge	*No Response*
LSN	*control-saline*	*16.7% (7)*	*76.2% (32)*
	sham	*14.3% (5)*	*77.2% (27)*
	lesion	*43.8% (7)**	*37.5% (6)**
HIPPOCAMPUS	*control-saline*	*47.8% (22)*	*45.6% (21)*
	sham	*30.0% (15)*	*66.0% (33)*
	lesion	*54.6% (12)**	*31.8% (7)**

** $p < 0.02$ against control-saline and sham groups. Neurons showing an inhibition of firing after DRN stimulation were discarded from analysis because of their lowest percentage. (DRN: dorsal raphe nucleus; LSN: lateral septal nucleus)*

Long-Term DMI Effects

In the septal and hippocampal afterdischarging neurons, the long-term treatment with DMI (2.14 mg/kg, i.p.; during 21 days) produced non significant changes in neuronal firing rate.

In the septal and hippocampal non-late responders neurons, long-term DMI produced different effects depending on early surgery and nucleus. In the septal neurons from sham lesion group, long-term DMI produced and increased rate of firing. On the contrary, in septal neurons recorded from early lesion group, DMI produced a significant decreased rate of firing (table 2).

Long-term DMI produced an increased rate of firing in

hippocampal neurons regardless of early surgery.

Microiontophoretic DMI Effects

In afterdischarging septal neurons from control group (non DMI-treated), DMI locally applied produced a smooth long-lasting increased firing rate, roughly reaching 25% from control recording. In those septal non-late responders neurons from control group, DMI also produced a very soft (in as much as 10%) increased firing rate (Fig. 1, upper panel).

TABLE 2

FIRING FREQUENCY (HZ) AFTER LONG-TERM DMI
(Non-late responder neurons)

	LSN	*HIPPOCAMPUS*
control-saline	*4.03±0.23*	*2.28±0.23*
sham	*7.54±0.80* **	*6.21±1.06* **
lesion	*1.90±0.37* **	*5.14±1.92* *

* *p < 0.05 and* ** *p < 0.01 against control-saline group.*

Long-term DMI produced changes in the response to DMI locally applied to septal neurons depending on early surgery and the kind of response to dorsal raphe nucleus stimulation. In the septal afterdischarging neurons from both the sham and lesion groups, the local administration of DMI produced no significant changes (Fig. 1, lower panel).

However, in septal non-late responder neurons from sham group, DMI produced the greatest observed change, consisting on a significant ($p < 0.05$) long-lasting (around 60 s) increased (about 150% from control) firing rate (Fig. 1, middle panel). An inverted response appeared in the septal non-late responders neurons from lesion group in which DMI given locally inhibited the firing rate.

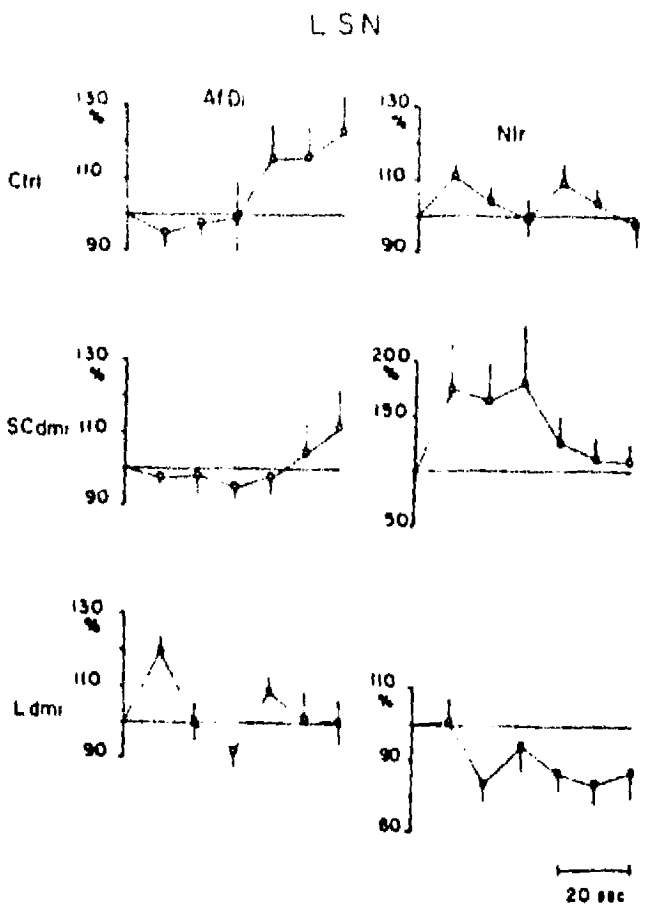

Figure 1. Response of afterdischarging (AfDi) and nonresponders (Nlr) lateral septal neurons to DMI microiontophoretically applied in control group (Ctrl), sham-lesion long term DMI treated group (Scdmi) and lesion group long-term DMI treated (Ldmi). Results are expressed as the percentage of change in neuronal firing rate from control recordings.

Similarly, the microiontophoretical DMI application produced changes in firing rate in hippocampal neurons depending on their kind of response to dorsal raphe nucleus stimulation. In control-non-DMI impregnated group, the local application of the tricyclic produced a decreased firing rate in hippocampal afterdischarging neurons. On the contrary, in hippocampal neurons non-late responders, DMI locally applied produced a short period of

increased rate of firing (Fig. 2, upper panel).

In the sham lesion group long-term treated with DMI, the local application of DMI produced an increased ($p < 0.04$) rate of firing in hippocampal afterdischarging neurons; and similar but longer response appeared in hippocampal neurons non late responders to dorsal raphe nucleus stimulation (Fig. 2, middle panel). The early lateral septal nucleus lesion, did not modify substantially the kind of response in hippocampal neurons.

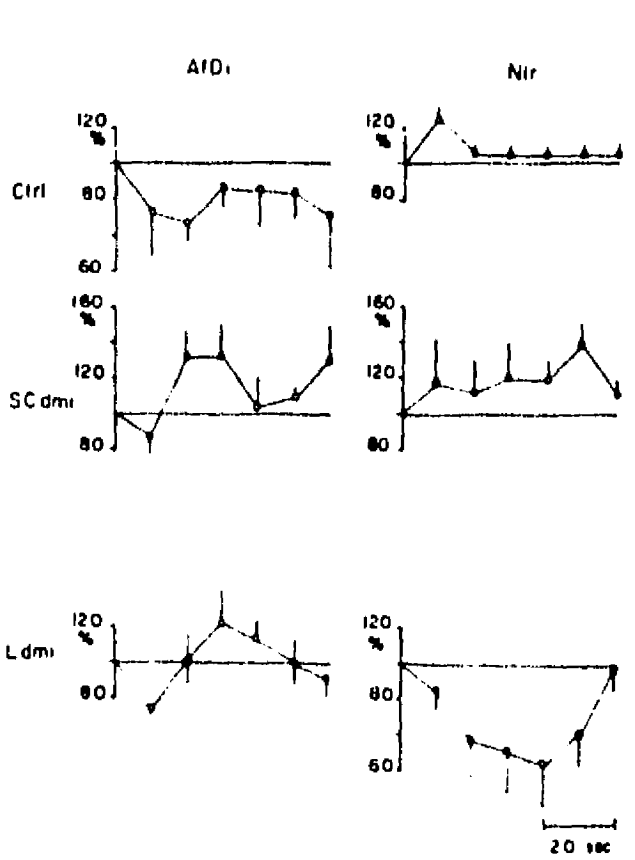

Figure 2. Response of hippocampal neurons (CA3) to DMI applied by microiontophoresis. Neurons are classified in regard to their response to dorsal raphe nucleus into those showing afterdischarge (AfDi), and non-responder (Nlr) in control, sham-lesion and lesion groups. Surgical groups received DMI (2.14 mg/Kg, 21 days, i.p.).

Discussion

It might be argued that different neuronal populations were recorded from control, sham or lesional groups. However, the depth of recordings (data not shown), as well as the amplitude of recordings varied in a non significant manner. Therefore, it is assumed that the recorded pool of neurons came from similar anatomical places in the different experimental groups, as confirmed by gross histology.

Early Septal Lesion Effects

Tricyclics as well as serotonin local application in the lateral septal nucleus produces mainly inhibition of firing (Jöels et al., 1985). In control non-DMI treated, as well as in the sham group the dominant kind of response to dorsal raphe nucleus stimulation appears to be the non-late responders in both the septal and the hippocampal neurons which suggests a dominant serotonergic innervation. However, in lesional septal or hippocampal neurons from lesion group, the dominant kind of active recorded neurons appeared for those responding with an afterdischarge which suggests that the early lesion, destroyed mainly the serotonergic endings coming from dorsal raphe nucleus; all of these may be related with a modified raphe-limbic innervation after early surgery, following probably an enriched spreading out of excitatory aminoacids innervation, which seems related with some behavioral disturbances, as described elsewhere (Contreras et al., 1995).

DMI Systemic Effects

Clomipramine is a tricyc.ic which produces an increased firing rate in those lateral septal neurons (Contreras et al., 1990) innervated by hippocampus (Marván et al., 1993). In present study the increased rate of firing after long-term DMI appeared only in septal neurons non-late responders to dorsal raphe nucleus stimulation which suggests sparsicity in the innervation from the dorsal raphe nucleus to the septal neurons responders to tricyclics with enhanced firing rate. However, an inverted effect appeared in lesional group, supporting the idea that some change in innervation occurred as a consequence of early lesion. In fact, the change in basal firing rate from lesional group proved to be similar than the hippocampal response, which certainly appeared unmodified by early lesion and agrees with results from other authors (Dijcks et al., 1991a).

Microiontophoretic DMI Effects

In septal non-late responders neurons, DMI given locally increased the firing rate in control and sham neurons. Another tricyclic, clomipramine applied to lateral ventricle produces an increased firing rate (Contreras et al., 1989), in agreement with present report. In the hippocampus, DMI locally applied produced an increased firing rate which, in turn, agrees with other reports (Dijcks et al, 1991a).

In lateral septal nucleus and hippocampus groups the early septal lesion affected the response to DMI given locally. In the hippocampal afterdischarging neurons, DMI given locally inhibited the firing rate in non-DMI treated group (Dijcks et al., 1990b);

however, long-term DMI related to an increase of firing rate in both sham and lesion groups (Dijcks et al., 1991a), suggesting at first that long-term DMI sensitizes local processes; and secondly, that only the afterdischarging neurons conserved their pharmacological properties.

Conclusion

The neurons from lateral septal nucleus and hippocampus innervated by raphe nucleus conserved their pharmacological properties after an early septal lesion but only for those neurons showing an afterdischarge which suggest a combined participation of neurotransmitters; whereas, raphe-limbic neurons showing only a paucisynaptic response but not late responses lost their properties to DMI stimulation. A change in the innervation patterns after early lesion as the background of behavioral and pharmacological changes in response is suggested.

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Discusión General

Septum Lateral y Acciones de los TAD.

Los resultados electrofisiológicos mas relevantes reportados en estos experimentos son: 1) la clorimipramina, la desmetilimipramina (antidepresivos tricíclicos), el electrochoque y la privación de sueño aguda total (tratamientos antidepresivos no farmacológicos) incrementan la frecuencia de disparo de las células del septum lateral. Es decir, tienen un efecto similar sobre la frecuencia de disparo neuronal de esta estructura límbica. Con estos resultados, se confirma el hallazgo de nuestro grupo de que uno de los sitios de acción de los TAD es el NSL. Sin embargo, también se encontró que la combinación de varios TAD carece de acciones sinergistas (165) además de que la privación de sueño aguda total es un tratamiento poco eficaz (137) y bloquea las acciones del electrochoque en el NSL.

Se ha sugerido la participación de las vías 5HT y NE en el mecanismo de acción de los TAD, ya que su administración crónica genera mecanismos plásticos compensadores que ocurren por su acción sostenida sobre los receptores sinápticos. De esta manera, se ha demostrado que los TAD administrados de forma crónica producen subsensibilidad de los receptores presinápticos, así como supersensibilidad de los receptores postsinápticos (10; 23; 156).

La CMI inhibe la recaptura de 5HT (216) y su administración aguda produce disminución del disparo de las células serotonérgicas de los núcleos del rafe (177). En tanto, que la DMI bloquea la recaptura de noradrenalina (75) y produce disminución del disparo

de las células noradrenérgicas del locus coeruleus (138). A pesar de que la aplicación de algunos antidepresivos tienen efectos preferenciales sobre los receptores de un neurotransmisor en particular, existe relación funcional entre los receptores de ambos neurotransmisores, ya que si se destruyen algunas de las terminales serotonérgicas o noradrenérgicas, no se observan estos cambios plásticos (69; 111).

El electrochoque de manera semejante a la DMI produce disminución de la Bmáx del receptor 5HT1A en el hipocampo (133; 134; 147) pero difieren en su acción en el receptor 5HT2, ya que el ECT incrementa su número y la DMI lo disminuye (134). Por otro lado, se ha sugerido a la privación de sueño como un tratamiento antidepresivo eficaz (210; 211; 212, 213, 214), sin embargo en un trabajo previo de nuestro grupo se ha demostrado que la privación de sueño aguda total tiene poca potencia antidepresiva (39).

En síntesis, los TAD modifican las características funcionales de las células serotonérgicas que parten del NRD y noradrenérgicas que parten del locus coeruleus y que terminan en estructuras límbicas (97). Esto ha conducido al estudio de las estructuras límbicas directamente conectadas con estos núcleos en cuanto a su participación en las acciones de los TAD. En efecto, la responsividad de las células piramidales del hipocampo a la 5HT se incrementa después del tratamiento crónico con antidepresivos tricíclicos (20; 42; 43) y con el electrochoque (44). Asimismo, la administración crónica de antidepresivos acentúa el efecto de la estimulación eléctrica de la vía serotonérgica que llega al

hipocampo (21; 22).

Los cuerpos celulares de las neuronas que contienen la mayor parte de la serotonina en el SNC se encuentran en los núcleos del rafe. La vía serotonérgica ascendente se origina en los núcleos rafe dorsal y medial. Estas fibras viajan por la parte más ventral del haz medial del cerebro anterior y se separan en un componente medial y en otro lateral. El componente medial asciende al área septal (8; 9). La inervación serotonérgica de los núcleos septales es abundante (57; 94) en el núcleo septal lateral (Figura 3).

La inervación noradrenérgica (Figura 4) del septum proviene principalmente de la vía dorsal noradrenérgica que se origina en el locus coeruleus y asciende por el haz medial del cerebro anterior (208) y llega principalmente a los núcleos septal medial/Banda Diagonal de Broca y septofimbrial (105). Se requiere de la integridad de la inervación noradrenérgica para que los antidepresivos puedan revertir los efectos conductuales presentados en modelos de depresión animal (187).

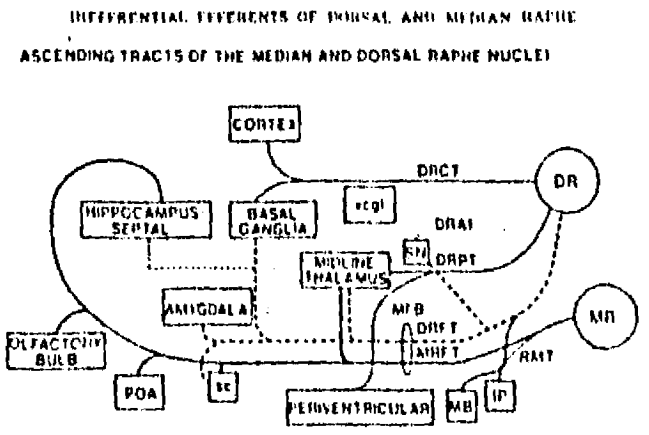

Figura 3.- Principales tractos serotonérgicos que parten del rafe dorsal (DR) y el rafe medial (MR) hacia diferentes estructuras del sistema límbico: tomado de Azmitia et al., 1978 (9).

En la presente tesis se encontró aumento en la frecuencia de disparo espontáneo de las células del NSL, producido por la administración crónica de varios TAD. Esto sugiere modificaciones a nivel de los receptores serotonérgicos postsinápticos de este núcleo, ya que la administración crónica de antidepresivos tricíclicos produce supersensibilidad de estos receptores (23).

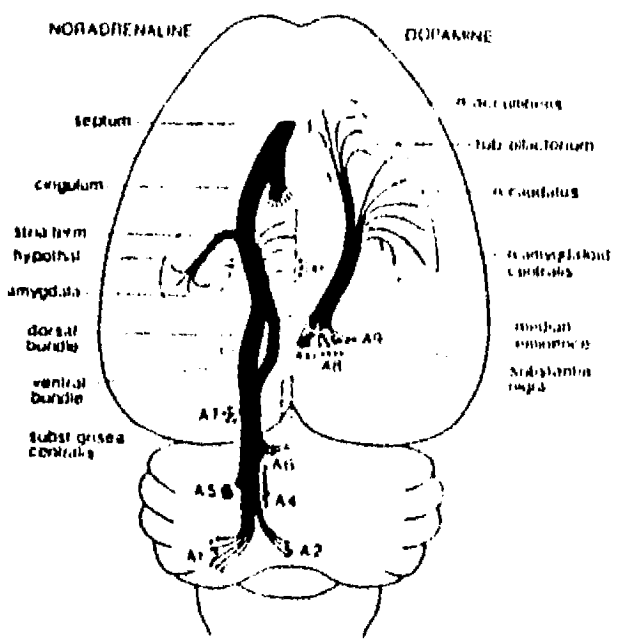

Figura 4.- Esquema de las proyecciones horizontales de las vías noradrenérgicas y dopaminérgicas ascendentes: tomado de Ungerstedt, 1971 (208).

Por otro lado, cabría esperar que los TAD que bloquean la recaptura de NE, como la desmetilimipramina y que afectan de manera predominante las vías noradrenérgicas, alteraran las características de los receptores del núcleo septal medial, el que a su vez tiene conexiones con el NSL (101), obteniéndose como resultado final, aumento de excitabilidad de las neuronas del NSL, de esta manera se alteraría la relación fisiológica que el septum lateral tiene con otras estructuras nerviosas (Figura 5). En efecto, en el septum lateral, la acetilcolina actúa en receptores

M1 y produce desinhibición por disminución de la liberación de GABA (74), esta inervación colinérgica proviene directamente de neuronas del septum medial (4), las que a su vez son inervadas por fibras noradrenérgicas provenientes del locus coeruleus (121).

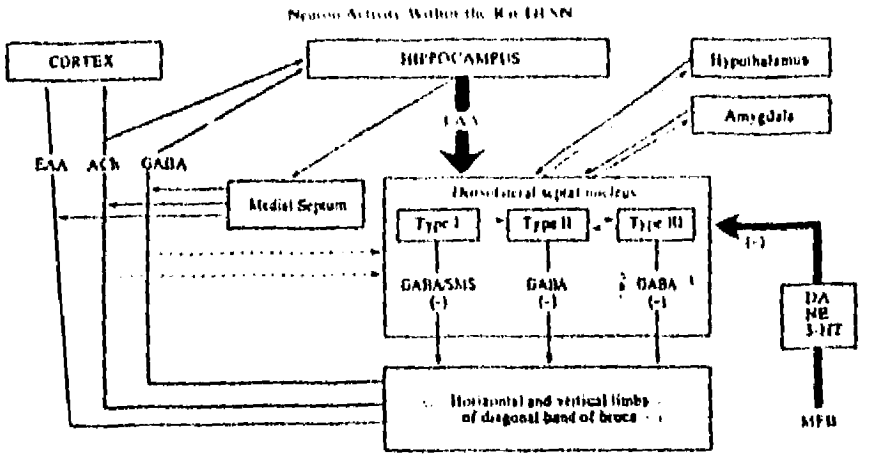

Figura 5.- Circuito de las conexiones intraseptales y las principales aferencias y eferencias del LSN con otras estructuras del sistema límbico, así como algunos neurotransmisores presentes en estas sinapsis: tomado de Gallagher et al., 1995 (59).

Los núcleos septales difieren de forma intrínseca y en sus conexiones, por lo que es de esperar distintas acciones de un mismo tratamiento dentro de ellos. La identificación de las células septales tanto en su relación con el hipocampo como con el NRD y con el locus coeruleus aportaría datos electrofisiológicos de su respuesta a los TAD.

¿Cuales son las neuronas del septum lateral que incrementan su frecuencia de disparo al aplicar los TAD? Es factible proponer que sean las somatoespinosas identificadas en el NSL (4; 153), ya que al estimular el hipocampo, estas células presentan excitación monosináptica de corta latencia y duración breve (117) que se puede deber a la liberación de aspartato y una inhibición posterior del

disparo que se puede deber a la acción de las fibras recurrentes GABAérgicas (Figura 6) que presentan estas neuronas (78), es decir se trata de un fenómeno de retroalimentación negativa. Nuestro grupo de investigación ha demostrado que neuronas septales con características electrofisiológicas similares a las descritas, responden con aumento de la frecuencia de disparo al aplicar antidepresivos (113).

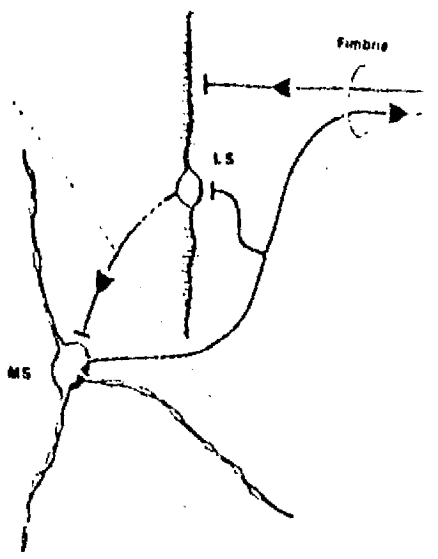

Figura 6 -Esquema en el cuál se ilustra que las fibras hipocampo-septales que corren por la fimbria terminan en espinas de neuronas del septum lateral (LS). Estas células poseen colaterales recurrentes y envían eferencias hacia neuronas del septum medial (MS). Las grandes neuronas colinérgicas del MS y otras envían fibras hacia el hipocampo. Asimismo los axones colinérgicos dan lugar a axones colaterales que inervan a las neuronas del septum lateral: tomado de Alonso et al., 1989 (4).

La participación del septum lateral en algunas de las acciones de los TADs es relevante, ya que participa en los estados hedónicos y en los fenómenos de autoestimulación, además de que al septum converge información de varias estructuras cerebrales y regula la actividad de otras como son el hipotálamo y el hipocampo.

De tal manera que es posible que una lesión septal temprana provoque depresión endógena con rasgos orgánicos, esto a su vez proporcionaría un modelo animal para estudiar las acciones de los TADs, además de que se conocerían los mecanismos plásticos subyecentes a la lesión del septum lateral y las acciones de los TAD.

Acciones de la Lesión Septal Temprana

La lesión septal temprana produjo mala ejecución de la prueba de nado forzado en los machos, en cambio las hembras tuvieron mejor ejecución de la prueba así como una mejor respuesta a la aplicación de los TAD que los machos. Y a nivel electrofisiológico, se encontró que las neuronas rafe- septales e hipocampales que tuvieron posdescarga conservaron sus propiedades funcionales, sin embargo, las neuronas rafe límbicas con respuesta pausisináptica perdieron su respuesta a la estimulación por DMI, lo cuál sugiere que en estas neuronas se presentó un cambio en los patrones de inervación provocados por la lesión septal temprana.

Si una de las acciones de los TAD es aumentar la frecuencia de disparo de las células del NSL (32; 34; 35; 37; 39) y si la lesión septal temprana afectó a las células del NSL que responden con aumento de la frecuencia de disparo al aplicar los antidepresivos, en especial de aquellas que se inhiben al estimular el hipocampo (113) y de aquellas que se excitan al estimular el NRD (36; 40) y si los deprimidos son incapaces de experimentar placer, entonces la lesión septal temprana produciría depresión endógena con rasgos orgánicos, fenómeno que se demostró en esta serie de experimentos,

además de que es dependiente del sexo de los animales.

Así, vemos que la lesión del septum, estructura que participa en los estados hedónicos y que exhibe una de las mayores densidades de neuronas que expresan mRNA para el receptor de andrógenos o estrógenos (182) y que ejerce en la conducta masculina influencia facilitatoria pero inhibitoria en la femenina (96), presenta mecanismos plásticos en compensación ante el efecto de lesiones. Pero, estos procesos plásticos pueden ser insuficientes y en consecuencia se producirían respuestas alteradas con la aplicación de TAD (155), lo que podría anular sus efectos antidepresivos (88), como sucedió en las hembras lesionadas. En cambio en los machos lesionados el efecto del tricíclico fué contrario con respecto a los controles. Esto es otro claro ejemplo de la existencia de dimorfismo sexual en el cerebro animal (25; 71; 100; 157; 167; 181).

Una de las posibles explicaciones de que la lesión haya afectado de forma diferente a las hembras que a los machos, se puede deber a la presencia de las hormonas ováricas: estradiol y progesterona. Ya que se ha visto que estos esteroides, cuando menos, en el hipotálamo (115; 116) y en el hipocampo (127) facilitan la regeneración sináptica después de lesiones. Por ejemplo, después de lesiones del sistema nervioso, la progesterona aumenta la supervivencia de neuronas (225, 226, 227) y los estrógenos incrementan el número de sinapsis en hembras ovariectomizadas (29) de forma dimorfica sexual (127).

Por otro lado, los estrógenos regulan la producción de factores de crecimiento neural (65; 186; 219), además de tener un efecto benéfico en la regeneración de los nervios periféricos y promover el crecimiento de neuritas en el hipotálamo y en la corteza cerebral (201; 202; 203; 204) de ratas adultas y en desarrollo (72; 108; 135; 191; 192).

En el NSL de hembras existen neuronas que concentran estrógenos (2; 152), los cuales incrementan el número de sinapsis (122), inducen reorganización de las membranas neuronales (61; 62; 63; 64; 142) y promueven la modificación de la producción de mRNA de los factores de crecimiento neural (186) en el hipocampo y en el septum (66). Esto sugiere que el septum de las hembras es plástico a la acción de las hormonas ováricas y regulan la acción de los TAD en el cerebro (162; 163; 166).

El sistema de receptores a los estrógenos está colocalisado con los factores de crecimiento neural en neuronas de roedores en desarrollo en el septum medial, en la banda diagonal, en la subtancia innominata, en el núcleo basalis de Meynert (123; 205), en la corteza cerebral, en el estriado y en el hipocampo (123), regiones en las que se ha descrito la presencia del factor de crecimiento neural (50; 95; 125; 199; 221; 222) y de neuronas que acumulan estrógenos (107; 206).

Por otro lado, en respuesta a lesiones cerebrales en ratas neonatas (81) existe reinervación colateral normal de fibras intactas lesionadas (160) pero también se puede presentar reinervación anormal, estos procesos de reinervación dependen del

estado de desarrollo del sistema nervioso al momento de producir la lesión (168). En ratas neonatas lesionadas de las vías noradrenérgicas existe hiperinervación noradrenérgica (93) y serotonérgica (14; 27; 185; 188). Asimismo, se ha demostrado que ante lesiones del septum, existe la producción de factor de crecimiento neural (31) y de sustancia P, los que promueven el crecimiento de fibras noradrenérgicas dañadas (82; 83; 84; 145).

Conclusiones

En esta tesis se confirma que el septum lateral de la rata es una estructura límbica que participa en las acciones de los TADs y que la lesión septal en etapas tempranas de la vida provoca cambios en su relación con otras estructuras límbicas y extralímbicas lo que implica alteraciones conductuales y farmacológicas en respuesta a la acción de los TAD.

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